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**VIA HAND DELIVERY**

Dockets Management Branch (HFA 305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: Citizen Petition to Establish that FDA Should Not Approve Abbreviated New Drug Applications ("ANDAs") or New Drug Applications under 505(b)(2) ("505(b)(2) NDAs") for Salmon Calcitonin Products Unless Certain Conditions Are Met**

**CITIZEN PETITION**

Dear Sir or Madam:

The undersigned submits this petition under the Federal Food, Drug, and Cosmetic Act ("FDC Act"), 21 U.S.C. § 355(j), and 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take the action below.

## A. Actions Requested

Petitioner asks that the Commissioner of Food and Drugs and the Food and Drug Administration ("FDA") not approve any Abbreviated New Drug Application ("ANDA") for a salmon calcitonin ("sCT") nasal spray citing Miacalcin® Nasal Spray ("Miacalcin") as the reference listed drug ("RLD") or any New Drug Application under section 505(b)(2) of the FDC Act ("505(b)(2) NDA") that relies on FDA's findings of safety and effectiveness for Miacalcin



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unless: (1) the active ingredient described in the ANDA or 505(b)(2) can be adequately demonstrated to be the "same" as that of the Miacalcin active ingredient; (2) the ANDA or 505(b)(2) NDA contains appropriate bioequivalence data using plasma concentration of salmon calcitonin and a suitable bioassay that bridge the ANDA or 505(b)(2) product to Miacalcin (unless the application contains new clinical and/or preclinical data to support differences between the ANDA or 505(b)(2) product and Miacalcin); and (3) the ANDA or 505(b)(2) NDA contains documented safety comparability to Miacalcin, including immunogenicity testing generated through a clinical study.

## B. Statement of Grounds

### 1. Proof of Sameness of the Active Ingredient and Adequacy of Bridging Information to Tie a Generic Product to the Safety and Efficacy of the RLD[1]

Section 505(j)(2)(A)(ii)(I) of the FDC Act requires that an ANDA for the approval of a new drug with a single active ingredient demonstrate, among other things, that the new drug has the "same" active ingredient as the approved innovator drug.[2] FDA's regulations state that an ANDA must include a statement that the active ingredient in the proposed product is the same as that in the RLD.[3] The ANDA regulations make no provision for the submission of additional data such as *in vitro*, animal, or clinical data for the determination of "sameness" of an active

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1 Although the terms "generic" and "RLD" apply strictly to the ANDA context, for simplicity, we will also use these terms to apply to 505(b)(2) NDAs that rely on FDA's findings of safety and effectiveness for a "listed drug."

2 21 U.S.C. § 355(j)(2)(A)(ii)(I).

3 21 C.F.R. § 314.94(a)(5)(i)(A).

ingredient.[4] For the reasons discussed below, a generic sCT product cannot be presumed to contain the "same" active ingredient as the innovator's chemically synthesized product, Miacalcin.

A generic sCT active ingredient, manufactured through chemical synthesis or through rDNA origin manufacturing, may not necessarily be the "same" as the RLD because the spectrum of impurities can be markedly different, thereby affecting the overall response to the product. The potential immunogenicity of proteins and peptides is of particular concern with this type of product, and must be assessed with thorough *in vitro* and *in vivo* testing. Because sCT is a 32 amino acid peptide and its identity to human calcitonin is only 50%, sCT has the potential for formation of anti-sCT antibodies following chronic administration.[5] In spite of a significant body of information about a specific active ingredient, generic peptide/protein products such as sCT nasal spray must undergo *in vitro* and *in vivo* immunogenicity testing to assess the potential for development of anti-sCT antibodies (for example) following chronic administration. Such testing will likely decrease the potential for unexpected immunological responses such as the one to erythropoietin that eventually led to the formation of pure red cell aplasia in a subset of

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[4] Moreover, clinical trials are not the preferred approach to establish bioavailability or bioequivalence in an ANDA, even though, in certain circumstances, the following approach may be used:

> Well-controlled clinical trials in humans that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence.

Id. § 320.24(b)(4).

[5] A Grauer et al. Exp. Clin. Endocrinol. 1995, 103:345-351.

patients[6] and avoid responses such as the formation of neutralizing antibodies that could prevent binding of, for example, sCT to cell receptors that would decrease efficacy of the sCT.

This requirement for *in vivo* immunogenicity testing should apply equally to chemically synthesized sCT or sCT manufactured through recombinant DNA technology. There are several reasons why it can not be assumed that the immunogenicity profile of a chemically synthesized protein molecule is the same as that of a chemically synthesized RLD solely on the basis of *in vitro* comparison. First, immune responses can be caused by differing levels of N-1 deletion peptides in the formulations. In solid phase peptide synthesis, each amino acid is added on to a growing chain one amino acid at a time. In the case of sCT, there are 32 amino acids, which means that the chemical synthesis requires 31 sequential additions of individual amino acids. At each step, the efficiency is something less than 100%. Therefore, at the end of the synthesis, an array of N-1 deletion contaminants may be present. These contaminants, which are difficult to remove by purification, may have immunogenic potential. Second, there can be varying levels of residual chemical contaminants present in different sCT active ingredients that could also contribute to the clinical effectiveness, immunogenicity or safety profile of the product. Third, differing levels of racemic mixtures in the formulations resulting during peptide synthesis (some D isomers may result during chemical synthesis) can cause immune responses. FDA has recognized the importance of these types of issues and has provided guidance regarding the contents of the CMC section of an ANDA or 505(b)(2) NDA where the active ingredient is a synthetically-produced peptide, stating that information pertaining to "[c]ertain biological

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6 N. Casadevall et al. J Am Soc Nephrol. 2005, 16 suppl 1:S67-9.

characteristics, such as potency, immunogenicity, or antigenicity may also be necessary."[7] Any ANDA or 505(b)(2) for an sCT product must contain the information described in the guidance document.

The potential for manufacturing-related formation of immunogenic contaminants discussed above (N-1 deletion proteins, residual contaminants, impurities or related substances, and levels of racemic mixtures) means that in addition to the CMC requirements, *in vitro* and *in vivo* immunogenicity testing must be required for any ANDA or 505(b)(2) drug that potentially will be administered chronically, in order to ensure both that the drug is safe and that the particular generic active ingredient maintains the same degree of efficacy over time. Without demonstrating the lack of neutralizing antibodies, there can be no assurance that the generic product is as effective as the RLD even though blood levels for the active ingredient may have been demonstrated to be comparable in comparative bioavailability studies.

Unless the applicant can demonstrate the sameness of the two sCT ingredients through appropriate testing, including immunological assays of samples obtained from subjects after adequate exposure to the product and data showing that the effects of the sCT on bone resorption are comparable to those of the innovator,[8] there can be no assurance that the active ingredients are the same. Due to the complex nature of proteins and peptides, and sCT in this particular case, FDA should not approve any ANDA or 505(b)(2) without accounting for the concerns identified in this petition.

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7 FDA, Guidance for the Industry for the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances, at 5 (Nov. 1994).

8 Petitioner notes that information of this sort was accepted by FDA to demonstrate sameness between Miacalcin and Fortical® Nasal Spray in a 505(b)(2) NDA. See Letter from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research, to Nancy L. Buc, Buc & Beardsley, Docket No. 2004P-0015/CP1, at 8-9 (Aug. 12, 2005).

### 2. Information Necessary for Approval of an sCT Product

Even if FDA determines that the sCT in an ANDA or 505(b)(2) NDA is the same as that in Miacalcin, Petitioner believes that the information and data requirements discussed below are also necessary for the approval of any sCT product.

First, certain preservatives are known to affect the bioavailability of drugs administered intranasally; for example, quaternary amines (detergents) have different effects on the bioavailability of proteins and peptides than methylparabens, benzyl alcohol, or chlorobutanol. This is particularly relevant in the case of salmon calcitonin because of low plasma concentrations, limits of detection (LOD) of available bioassays, and intrasubject variability. In addition, changes in the generic product formulation (including impurities and degradants) compared to RLD formulation, administered intranasally, can have an impact on local safety of the product. The effect of any preservative used in the formulation on the bioavailability and safety profile of the peptide must therefore be examined in appropriate clinical studies. Demonstration of equivalence through *in vitro* methods such as spray pattern, plume geometry, and osmolality is insufficient to prove that the bioavailability of the generic formulation will be equivalent or comparable to that of the RLD. FDA has provided guidance for all NDA and ANDA products that utilize nasal spray as a form of drug delivery.[9] Any ANDA or 505(b)(2) NDA that references Miacalcin should therefore contain all CMC information described in the guidance document.

Second, testing of the identity of the active ingredient is insufficient to establish the biological potency or bioactivity of a protein or peptide based drug. For peptides and complex

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[9] FDA, Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation (July 2002).

molecules, comparable biologic activity to the RLD must be demonstrated since standard analytical techniques do not confirm biological activity. The confirmation of biological activity should be mandated for peptides manufactured by either chemical synthesis or recombinant DNA technology. If an application for an sCT product does not contain information regarding a suitable bioassay for release of the active ingredient and for monitoring of the finished product during stability testing, the submission must be considered incomplete.

Third, even if the ANDA or 505(b)(2) NDA can demonstrate sameness and bioequivalence and contains an appropriate bioassay, the safety profile of the sCT active ingredient cannot be presumed. An application for a nasal spray that contains any inactive ingredients or impurities/degradants different from those in the RLD must contain information demonstrating that the difference does not affect the safety and/or effectiveness of the drug product.[10] Potential issues regarding immunogenicity of the final formulation may arise due to the inactive ingredients used in a generic sCT product. Immune responses can be caused by different levels of leachates in the final formulation. This is particularly important since different excipients can induce different leachates from components of the final container and/or closure system. In fact, recent information indicates that leachates from the uncoated rubber components of pre-filled erythropoietin syringes may have acted as adjuvants that increased the immunogenicity of erythropoietin.[11] It has been speculated that the presence of the leachates in this instance may have resulted in or contributed to the formation of neutralizing antibodies and eventually led to the formation of pure red cell aplasia in a subset of patients. Therefore, because the testing necessary to establish bioequivalence would be insufficient to address potential

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[10] See, e.g., 21 C.F.R. § 314.94(a)(9)(v); FDA, Guidance for Industry, Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients, at 3 (May 2005).

[11] N. Casadevall et al. J Am Soc Nephrol. 2005, 16 suppl 1:S67-9.

immunogenicity issues, it is essential that thorough safety testing, including a clinical study examining the comparative immunogenicity of the proposed product and Miacalcin (e.g., binding and neutralizing antibody formation), be performed.

Furthermore, certain inactive ingredients, such as chlorobutanol and benzalkonium chloride, which might be used in the formulations of generic sCT nasal spray products, should not exceed the maximum daily amount as provided in other approved drug products without satisfactory proof of safety.[12]

### 3. Conclusion

Because it is not clear without scientific evidence that one sCT active ingredient is the same as another, even when both are manufactured through chemical synthesis, no application for an sCT nasal spray should be approved unless it contains appropriate scientific data to confirm the sameness of the sCT ingredients, bioequivalence data using plasma concentration levels of salmon calcitonin, a suitable bioassay and immunogenicity testing generated through a clinical study. Such data are necessary to bridge the particular proposed generic sCT product to the Miacalcin approval.

## C. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31(a).

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[12] See, e.g., FDA, CDER, Inactive Ingredient Search for Approved Drug Products, available at http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

**D. Economic Impact**

Petitioner will submit economic impact information upon request of the Commissioner.

**E. Certification**

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Respectfully submitted,

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